Psychopharmacology (1989) 99:151–155

Psychopharmacology

SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade?

E. Acquas, E. Carboni, P. Leone, and G. Di Chiara
Institute of Experimental Pharmacology and Toxicology, University of Cagliari, Viale A. Diaz 182, I-09125 Cagliari, Italy

Abstract. The influence of the D_1 antagonist SCH 23390 on the motivational properties of rewarding (morphine, nicotine and diazepam) and aversive (naloxone, phencyclidine and picrotoxin) drugs was studied in the rat in a two-compartment place-conditioning paradigm, which included a pre-conditioning test for spontaneous place-preference. The specific D_1 dopamine-receptor antagonist SCH 23390 (0.05 mg/kg SC), paired with both compartments or, separately, with the preferred or with the non-preferred compartment, failed to affect the spontaneous unconditioned preference of the animal. Pairing of morphine (1.0 mg/kg SC), nicotine (0.6 mg/kg SC) or diazepam (1.0 mg/kg IP) with the less preferred compartment induced significant preference for that compartment. Pairing of SCH 23390 (0.05 mg/kg SC) with both compartments completely blocked the place-preference induced by morphine, nicotine and diazepam. Naloxone (0.8 mg/kg SC), phencyclidine (2.5 mg/kg SC) or picrotoxin (2.0 mg/kg IP) paired with the preferred compartment elicited place-aversion. Pairing of SCH 23390 (0.05 mg/kg SC) with both compartments abolished also the place-aversion induced by naloxone, phencyclidine and picrotoxin. The results indicate that blockade of dopamine transmission blocks the motivational properties of rewarding as well as aversive stimuli. It is suggested that neuroleptics rather than simply blocking the rewarding impact of positive reinforcers (anhedonia, lack of pleasure) exert a more general influence on conditioned behaviour by blocking the affective impact of negative as well as positive reinforcers (apathy, lack of motivation).

Key words: Dopamine – Morphine – Nicotine – Diazepam – Naloxone – Phencyclidine – Picrotoxin – Place-aversion – Place-preference – SCH 23390

Central dopamine (DA) is currently regarded to play a key role in unconditioned as well as in conditioned behaviour. In fact, DA receptor blockers exert profound effects on operant behaviour which have been attributed to an impairement of performance as well as motivation (Liebmann 1983). In particular, it has been postulated that neuroleptics interfere with the reinforcing impact of unconditioned stimuli ("anhedonia") and that dopamine mediates the pleasurable quality of reinforcement (Wise 1983).

However, an alternative explanation is that neuroleptics impair the stimulus control of behaviour independently from the motivational quality, positive or negative, of the stimulus (Dews and Morse 1961). In agreement with this, neuroleptics block the efficacy of negatively reinforcing stimuli in a conditioned avoidance paradigm (Liebman 1983).

In agreement with this possibility neuroleptics block the efficacy of negatively reinforcing stimuli in a conditioned avoidance paradigm (Liebman 1983). Unfortunately, however, the theoretical impact of these observations is attenuated by the possibility that the effects of neuroleptics on conditioned avoidance are in part or entirely attributable to a deficit in performance rather than motivation (Bignami 1978; Grilly et al. 1984). Moreover, in a conditioned avoidance paradigm an anhedonia mechanism cannot be excluded, as the behaviour could be maintained by positive reinforcement via feedback safety signals (Mackintosh 1974).

Place-conditioning can be utilized for studying the motivational properties of drug stimuli and is based on the fact that animals prefer environmental stimuli paired with positive reinforcers (place-preference) and avoid environmental stimuli paired with negative reinforcers (place-aversion) (Garcia et al. 1957). Depending on the drug, palce-preference (Rossi and Reid 1976; Reicher and Holman 1977; Katz and Gormezano 1979; Sherman et al. 1980; Bozarth and Wise 1981; Spyraki et al. 1982a, b; Fudala et al. 1985) or place-aversion (Mucha et al. 1982; Mucha and Iversen 1984; Barr et al. 1985; Spyraki et al. 1985; Iwamoto 1986) is obtained. In agreement with the notion that DA is essential for the rewarding properties of drug stimuli, blockade of DA-receptors has been reported to reduce or to abolish the place-preference conditioning induced by amphetamine and opiates (Bozarth and Wise 1981; Spyraki et al. 1983; Leone and Di Chiara 1987). Other studies, however, have failed to otain an impairment of drug-reward with neuroleptics (Spyraki et al. 1982; Mackey and Van der Kooy 1984; Martin-Iverson et al. 1984). Biochemical data in favour of the DA hypothesis of drug reward have been recently provided by us using brain dialysis in freely moving rats. Thus it has been shown that drugs of abuse belonging to widely different categories (ethanol, amphetamine, cocaine, morphine, nicotine and phencyclidine) share the property of stimulating DA-release preferentially in the n. accumbens as compared to the dorsal caudate (Imperato and Di Chiara 1986; Imperato et al. 1986; Di Chiara and Imperato 1986; Di Chiara et al. 1987; Di Chiara and Imperato 1988a, b). In order to further evaluate the role of DA in motivation we have studied the effect of blockade of DA transmission by the D_1 antagonist SCH 23390 (Iorio et al. 1983; Hyttel 1983) on the place conditioning elicited

Offprint requests to: G. Di Chiara

by drugs with aversive or with rewarding properties such as naloxone (Mucha and Iversen 1984; Spyraki et al. 1985) phencyclidine (Barr et al. 1985; Iwamoto 1986) and picrotoxin (Spyraki et al. 1985) or morphine (Rossi and Reid 1976; Sherman et al. 1980; Mucha et al. 1982), nicotine (Fudala et al. 1985) and diazepam (Spyraki et al. 1985).

Materials and methods

Animals. Male Sprague-Dawley rats (Charles River, Calco, Italy) weighing 200–250 g were used. The rats were housed in groups of six with water and food available ad lib. under an artificial 12 h light dark cycle (lights at 6.00 a.m.) and constant temperature (22° C) and relative humidity (60%).

Apparatus. The apparatus consisted of two square-base Plexiglas compartments (h 38 × 30 × 30 cm) one with white and the other with grey walls and transparent covers, separated by guillotine doors. The apparatus was placed in a soundproof room with white noise and constant light provided by a 40 W lamp placed above the compartment.

Procedure. Each experiment was performed over 8 days and was composed of three phases. During the first phase (pre-conditioning) rats were given access to both compartments of the apparatus for 15 min each day for the 2 days. On day 3, the time spent by the rat in each compartment was recorded. This time indicates the "unconditioned" preference of the rat for each compartment. The second phase (conditioning) had a duration of 4 days during which the rats were administered drugs or vehicle. In order to study place-preference, the rats were exposed for 30 min or for 1 h (depending of the drug) to the non-preferred compartment after administration of the drug and after an interval of 4 h to the preferred compartment after administration of saline; care was to balance the order of exposures to each compartment. During the third phase (post-conditioning), on day 8 the guillotine door separating the two compartments was removed and the time spent by the rat in each compartment was recorded during 15 min (900 s) of observation. The difference in seconds between the time spent in the drug-paired compartment in the post-conditioning test and that spent in the pre-conditioning one is a measure of the degree of conditioning induced by the drug. If this difference is positive then the drug has induced a preference for the drug paired compartment, while the opposite indicates the induction of an aversion.

Drugs. The control rats received two SC injections of saline, one 10 min and the other immediately before exposure to the white or grey compartment, i.e. during the 4 days of conditioning. To study the effect of drugs on place-conditioning, the drugs, dissolved in saline were given SC (0.1 ml/100 g) immediately before placing the rats in the compartment. To study the effect of SCH 23390 (0.05 mg/kg SC in saline) alone or in combination with the drugs, the antagonist was given in place of the 10 min saline injection. SCH 23390 was paired with both compartments. Morphine HCl, nicotine hydrogen tartrate, naloxone HCl (Sigma) and picrotoxin (Sigma) were dissolved in saline. Diazepam (Valium, Roche) and phencyclidine hydrochloride (Sernylan, Bio-Ceutic Laboratories Inc., St Joseph, Miss., USA) were diluted with saline from concentrated solutions.

Statistics. The significance of differences between the preference in the pre-conditioning trial and in the drug conditioned one was evaluated by two-way ANOVA followed by post hoc Newman-Keuls test.

Results

Saline and SCH 23390

As shown in Figs. 1 and 2 conditioning with saline paired with both sides of the box, failed to alter side-preference. SCH 23390 paired with both sides also failed to modify side-preference at dose of 0.05 mg/kg SC [$F(1.8)=1.85$, $P>0.05$]. In order to investigate if SCH 23390 by itself is capable of intrinsic motivational properties in the place-conditioning paradigm, we paired SCH 23390 (0.05 mg/kg SC) with the preferred environment and, in other rats, with the non-preferred environment. SCH 23390 failed to shift the spontaneous side-preference of the rats when paired with the preferred [$F(1,14)=2.45$, $P=0.13$], or with the non-preferred compartment [$F(1,18)=0.12$, $P=0.6$].

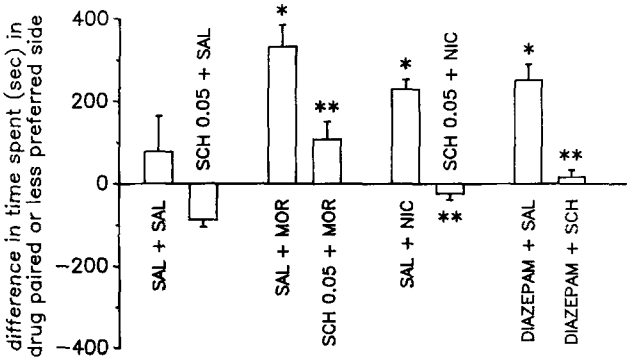

Fig. 1. Effect of SCH 23390 0.05 mg/kg SC on side preference induced by morphine (*MOR*) (1.0 mg/kg SC), nicotine (*NIC*) (0.6 mg/kg SC) and diazepam (*DIAZEPAM*) (1.0 mg/kg IP) paired with the less preferred compartment. Results indicate the mean (±SEM) of differences in time (s) spent in the drug-paired or in the less preferred compartment (saline conditioning) in the pre- and post-conditioning test (side-preference shift). *$P<0.05$ for shift in side-preference (Newman-Keuls); **$P<0.05$ for differences in the shift in side-preference (Newman-Keuls)

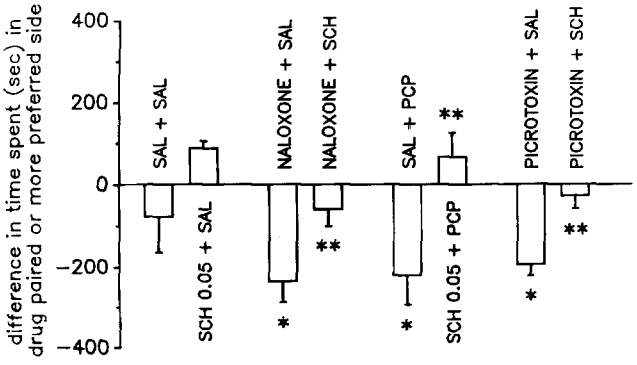

Fig. 2. Effect of SCH 23390 (0.05 mg/kg SC) on side-preference conditioned by naloxone (*NALOXONE*) (0.8 mg/kg SC), phencyclidine (*PCP*) (2.5 mg/kg SC) and picrotoxin (*PICROTOXIN*) (2.0 mg/kg IP) paired with the preferred compartment. Results are expressed as the mean (±SEM) side-preference shift (s) for the drug-paired or for the more preferred compartment (saline conditioning). *$P<0.05$ for shift in side preference (Newman-Keuls); **$P<0.05$ for differences in the shift in side-preference (Newman-Keuls)

Morphine

As shown in Fig. 1, morphine, at doses of 1.0 mg/kg SC, paired with the less-preferred compartment, induced place-preference; rats showed a significant difference in side-preference between pre- and post-conditioning test [$F(1.18) = 32.29$, $P < 0.005$)]. In agreement with previous results (Leone and Di Chiara 1987), SCH 23390 (0.05 mg/kg SC) paired with both compartments prevented morphine-induced place-preference conditioning, as indicated by the non significant difference in side-preference between pre- and post-conditioning tests [$F(1,8) = 3.59$, $P > 0.005$]. Two-way ANOVA of the difference in side-preference between pre- and post-conditioning tests yielded a significant main effect of Group [$F(3,20) = 7.88$, $P < 0.001$]; Newman-Keuls post hoc analysis showed a significant difference between saline and morphine ($P < 0.05$) and between saline + morphine and SCH 23390 + morphine ($P < 0.05$).

Nicotine

As shown in Fig. 1, nicotine, at the dose of 0.6 mg/kg SC, elicited place-preference when paired with the non-preferred compartment under strongly biased conditions (80% or more of the time spent in one compartment in the pre-conditioning test) [$F(1,8) = 16.50$, $P < 0.005$]. Pairing of SCH 23390 (0.05 mg/kg SC) with both compartments completely prevented nicotine-induced place-preference; thus, rats showed a non-significant difference in side-preference between pre- and post-conditioning test [$F(1,8) = 0.27$, $P > 0.05$]. Two-way ANOVA of the shift in side-preference between pre- and post-conditioning test yielded a significant main effect of Group under highly biased conditions [$F(3,14) = 7.49$, $P < 0.005$]; Newman-Keuls post-hoc analysis showed a significant difference between saline and nicotine-injected animals under strongly biased conditions ($P < 0.05$) and between saline + nicotine and SCH 23390 + nicotine ($P < 0.05$). In agreement with Clarke and Fibiger (1987), nicotine (0.6 mg/kg SC) failed to induce significant place-preference under unbiased pre-conditioning conditions [$F(1,8) = 0.27$, $P = 0.6$].

Diazepam

As shown in Fig. 1, in agreement with Spyraki et al. (1985), pairing of diazepam (1.0 mg/kg IP) with the non-preferred compartment induced place-preference as shown by the significant difference in side-preference between pre- and post-conditioning tests [$F(1,18) = 33.60$; $P < 0.001$]. SCH 23390 (0.05 mg/kg SC) paired with both compartments prevented diazepam-induced place-preference conditioning as indicated by the non-significant differences in side-preference between pre- and post-conditioning tests [$F(1,18) = 0.05$, $P > 0.05$]. Two-way ANOVA of the differences between pre- and post-conditioning tests yielded a significant Group effect [$F(3.26) = 11.35$, $P < 0.001$]; Newman-Keuls post-hoc analysis showed a significant difference between saline and diazepam ($P < 0.05$) and between saline + diazepam and diazepam + SCH 23390 ($P < 0.05$).

Naloxone

As shown in Fig. 2, and in agreement with Mucha et al. (1984), pairing of naloxone (0.8 mg/kg SC) with the preferred compartment resulted in place-aversion [$F(1,16) = 27.44$, $P < 0.005$]. SCH 23390 (0.05 mg/kg SC) paired with both compartments abolished naloxone induced place-aversion as indicated by the non-significant difference between pre- and post-conditioning tests [$F(1,18) = 3.06$, $P > 0.05$]. Two-way ANOVA yielded a significant difference between groups [$F(3,25) = 6.50$, $P < 0.003$]; post-hoc analysis showed significant differences between saline and naloxone ($P < 0.05$) and between saline + naloxone and SCH 23390 + naloxone ($P < 0.05$).

Phencyclidine

As shown in Fig. 2, pairing of phencyclidine (2.5 mg/kg SC) with the preferred compartment resulted in place-aversion [$F(1,8) = 13.02$, $P < 0.005$]. SCH 23390 (0.05 mg/kg SC) paired with both compartments strongly reduced the place-aversion induced by phencyclidine; rats showed a non-significant difference between pre- and post-conditioning [$F(1,8) = 1.29$, $P > 0.05$]. Two-way ANOVA yielded a significant difference between the groups [$F(3,16) = 5.06$, $P < 0.001$]; Newman-Keuls post-hoc analysis indicated significant differences between saline and phencyclidine-injected animals ($P < 0.05$) and between saline + phencyclidine and SCH 23390 + phencyclidine ($P < 0.05$).

Picrotoxin

As shown in Fig. 2 and in agreement with Spyraki et al. (1985), pairing of picrotoxin (2.0 mg/kg IP) with the preferred compartment resulted in a negative side preference shift, i.e. place-aversion, [$F(1,18) = 31.01$, $P < 0.001$]. SCH 23390 (0.05 mg/kg SC) paired with both compartments abolished picrotoxin-induced place-aversion as indicated by the lack of side preference shift [$F(1,18) = 3.07$, $P > 0.05$]. Two-way ANOVA yielded a significant difference between groups [$F(3,31) = 6.48$, $P < 0.001$]; post-hoc analysis showed significant differences between saline and picrotoxin ($P < 0.05$) and between saline + picrotoxin and SCH 23390 + picrotoxin ($P < 0.05$).

Discussion

Our results show that blockade of D_1 receptors by low doses of SCH 23390 reduces drug-conditioned place-preference as well as drug-conditioned place-aversion. In fact, SCH 23390 pretreatment, paired with both compartments, while failed to modify spontaneous side-preference, abolished morphine-, nicotine- and diazepam-induced place-preference as well as naloxone-, phencyclidine and picrotoxin- induced place-aversion. The results obtained here with morphine thus confirm our previous data using a place-preference procedure not involving a pre-conditioning test (Leone and Di Chiara 1987). As SCH 23390 is a potent and specific antagonist of D_1 DA receptors (Iorio et al. 1983; Hyttel et al. 1983), its effects on drug conditioned place-preference are likely to result from impaired DA transmission. An eventual mediation of SCH 23390 effects by the blockade of $5HT_2$ receptors is highly unlikely, as metergoline, a potent 5HT antagonist, failed to duplicate the effects of SCH 23390 (Di Chiara et al. in preparation). On the other hand the ability of blocking drug-conditioned place-aversion and place-preference does not seem to be specific for SCH 23390, as other DA receptor blockers, which act on another DA-receptor subtype (D_2), have been reported to impair drug-induced place-preference (Bozarth

and Wise 1981; Spyraki et al. 1983; Leone and Di Chiara 1987) as well as place-aversion (Iwamoto 1986).

The effect of SCH 23390 on the motivational properties of the drugs studied does not seem to result from the non-specific motivational effects of SCH 23390 itself: in fact, SCH 23390 failed to alter side-preference when specifically paired with one compartment.

The place-preference effects of nicotine are debated and require some comment. Fudala et al., (1985), obtained place-conditioning in a biased condition by pairing nicotine with the less preferred compartment, while Clarke and Fibiger (1987) failed to obtain place-conditioning with this drug in unbiased conditions.

Our results might explain these discrepancies, since they show that the ability of nicotine to elicit place-preference depends on the spontaneous preference of the animals: thus, place-preference can be clearly shown only in rats with a strong spontaneous preference for one compartment and by pairing the drug with the less preferred compartment.

This property of nicotine is rather puzzling if one considers that morphine, cocaine and amphetamine, three well known reinforcers, elicit place-preference in biased as well as in unbiased conditions (Spyraki et al. 1982a, b; Mackey and Van der Kooy 1984; Mucha and Iversen 1984). If one excludes other mechanisms (e.g. state-dependent learning), a simple explanation of the difficulty of demonstrating a place-preference effect of nicotine in unbiased conditions is that this drug is not a particularly strong reinforcer. Inasmuch as the place-preference conditioning induced by the drugs investigated by us is dependent upon their motivational properties (Mucha et al. 1982; Blander et al. 1984; Mucha and Iversen 1984; Bardo et al. 1984), the effect of SCH 23390 might be explained as being due to an interference with the reinforcing efficacy (positive or negative) of the drugs. In the case of positively reinforcing stimuli (morphine, nicotine and diazepam) the effect of SCH 23390 can be explained by postulating that the antagonist attenuates the rewarding impact of the stimulus ("anhedonia"), (Wise 1983) and is in agreement with the ability of SCH 23390 to block operant responding (Nakajima 1986), rewarding brain stimulation (Nakajima and McKenzie 1986; Sanger 1987), place-preference induced by morphine and amphetamine (Leone and Di Chiara 1987), food-rewarded operant responding, (Beninger et al. 1987) and cocaine-induced reward (Koob et al. 1987). However, an interference of SCH 23390 with the rewarding impact of the stimulus does not explain its effects on negatively reinforcing (aversive) stimuli such as naloxone, phencyclidine and picrotoxin. These might instead be postulated to be due to an impairment of the aversive properties of the stimulus. It appears therefore, that SCH 23390 blocks both rewarding as well as aversive motivational influences, as postulated by Dews and Morse (1961) for neuroleptics in general.

Since SCH 23390 is a potent D_1 antagonist, these results suggest that DA is necessary for operant behaviour not simply (or not even) because it mediates reward but because it is essential for conferring motivational relevance (and therefore significance in terms of conditioning) to stimuli irrespective of their negative (aversive) or positive (rewarding) quality. Accordingly, lack of DA rather than "anhedonia" (lack of pleasure) would result in lack of motivation; within this frame work, "anhedonia" would be just one expression of a more general disturbance of motivation.

The present hypothesis fully agrees with the well known effect of neuroleptics in man. These drugs have been described to reduce not only the "euphoria" but also the "dysphoric" effects of psychoactive drugs; moreover, neuroleptics are known to reduce the affective impact of negative as well as positive stimuli in man (Belmaker and Wald 1977; Baldessarini 1980). Most relevant to this issue is the description given in 1952 by Delay and Deniker (Delay and Deniker 1952) of the effect of chlorpromazine in man: "apparent indifference, slowing of responses to external stimuli, diminution of initiative and of anxiety". On this basis neuroleptic-induced lack of motivation might be regarded as a form of "apathy" (lack of motivation) rather than of "anhedonia" (lack of pleasure).

References

Baldessarini RJ (1980) Drugs and the treatment of psychiatric disorders. In: Goodman Gilman A, Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics, 6th edn. Mac Millan, New York, pp 395–418

Bardo MT, Miller JS, Neisewander JS (1984) Conditioned place preference with morphine: the effect of extinction training on the reinforcing CR. Pharmacol Biochem Behav 21:545–549

Bardo MT, Neisewander JL, Miller JS (1986) Repeated testing attenuates conditioned place-preference with cocaine. Psychopharmacology 89:239–243

Barr GA, Paredes W, Bridger WH (1985) Place conditioning with morphine and phencyclidine: dose dependent effects. Life Sci 36:363–368

Belmaker RH, Wald D (1977) Haloperidol in normals. Bri J Psychiatry 131:222–223

Bignami G (1978) Effects of neuroleptics, ethanol, hypnotic-sedatives, tranquilizers, narcotics and minor stimulants in aversive paradigms. In: Anisman H, Bignami G (eds) Psychopharmacology of aversively motivated behaviour. Plenum Press, New York, pp 385–402

Blander A, Hunt T, Blair R, Amit Z (1984) Conditioned place preference: an evaluation of morphine's positive reinforcing properties. Psychopharmacology 84:124–127

Benninger RJ, Cheng M, Hahn BL, Hoffman DC, Mazurski EJ, Morency MA, Ramm P, Stewart RJ (1987) Effects of extinction, pimozide, SCH 23390, and metoclopramide on food-rewarded operant responding of rats. Psychopharmacology 92:343–349

Bozarth MA, Wise RA (1981) Heroin reward is dependent on a dopaminergic substrate. Life Sci 29:1881–1886

Clarke PBS, Fibiger NC (1987) Apparent absence of nicotine-induced conditioned place-preference in rats. Psychopharmacology 92:84–88

Delay J, Deniker P (1952) I° Congrès des Al et Neurol de Langue Fr. In: Compte rendu du Congrès. Masson et Cie, Paris

Dews PB, Morse WH (1961) Behavioural pharmacology. Ann Rev Pharmacol 1:145–174

Di Chiara G, Imperato A (1986) Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with trans-cerebral dialysis in freely moving rats. Ann NY Acad Sci 473:367–381

Di Chiara G, Imperato A (1988a) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 85:5274–5278

Di Chiara G, Imperato A (1988b) Opposite effects of μ and k-opiate agonists on dopamine-release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J Pharmacol Exp Ther 244:1067

Di Chiara G, Imperato A, Mulas A (1987) Preferential stimulation of dopamine release in the mesolimbic system: a common fea-

ture of drugs of abuse. In: M. Sandler et al. (eds) Neurotransmitter interactions in the basal ganglia. Raven Press, New York, pp 171–182

Fudala PJ, Teoh KW, Iwamoto ET (1985) Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol Biochem Behav 22:237–241

Garcia J, Kimeldorf DJ, Hunt EL (1957) Spatial avoidance in the rat as a result of exposure to ionizing radiation. Br J Radiat 30:318–321

Grilly DM, Johnson SK, Minardo R, Jacoby D, LaRiccia J (1984) How do tranquilizing agents selectively inhibit conditioned avoidance responding? Psychopharmacology 84:262–267

Hyttel J (1983) SCH 23390 the first selective dopamine D_1 antagonist. Eur J Pharmacol 91:153

Imperato A, Di Chiara G (1986) Preferential stimulation of dopamine-release in the nucleus accumbens of freely moving rats by ethanol. J Pharmacol Exp Ther 239:219–228

Imperato A, Mulas A, Di Chiara G (1986) Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol 132:337

Iorio LC, Barnett A, Leitz FH, Houser VP, Korduba CA (1983) SCH 23390, a potential benzazepine antipsycotic with unique interactions on dopaminergic systems. J Pharmacol Exp Ther 226:462

Iwamoto ET (1986) Place-aversion conditioned by phencyclidine in rats: development of tolerance and pharmacologic antagonism. Alcohol Drugs Res 6:265–276

Katz RJ, Gormezano G (1979) A rapid and inexpensive technique for assessing the reinforcing effects of opiate drugs. Pharmacol Biochem Behav 11:231–233

Koob GF, Le HT, Creese I (1987) The D_1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in rat. Neurosci Lett 79:315–320

Leone P, Di Chiara G (1987) Blockade of D-1 receptors by SCH 23390 antagonizes morphine- and amphetamine-induced place preference conditioning. Eur J Pharmacol 135:251

Liebman JM (1983) Discriminating between reward and performance: a critical review of intracranial self-stimulation methodology. Neurosci Biobehav Rev 7:45–72

Mackey WB, Van der Kooy D (1984) Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. Pharmacol Biochem Behav 22:101–105

Mackintosh NJ (1974) A theory of attention: variation on the associability of stimuli with reinforcement. The psychology of animal learning. Academic Press, London

Martin-Iversen MT, Ortman R, Fibiger HC (1984) Place preference conditioning with methylphenidate and nomifensine. Brain Res 332:59–67

Mucha RF, Iversen SD (1984) Reinforcing properties of morphine and naloxone revealed by conditioned place preference: a procedural examination. Psychopharmacology 82:241–247

Mucha RF, Van der Kooy D, O'Shaughnessy M, Bucenieks P (1982) Drug reinforcement studied by the use of place conditioning in rat. Brain Res 243:91–105

Nakajima S (1986) Suppression of operant responding in the rat by dopamine D_1 receptor blockade with SCH 23390. Physiology 14:111–114

Nakajima S, MacKenzie GM (1986) Reduction of the rewarding effect of brain stimultion by blockade of dopamine D_1 receptor with SCH 23390. Pharmacol Biochem Behav 24:919–923

Reicher MA, Holman EW (1977) Location preference and flavor aversion reinforced by amphetamine in rats. Anim Learn Behav 5:343–346

Rossi NA, Reid LD (1976) Affective states associated with morphine injections. Physiol Psychol 4:269–274

Sanger DJ (1987) The actions of SCH 23390, a D_1 receptor antagonist, on operant and avoidance behavior in rats. Pharmacol Biochem Behav 26:509–513

Sherman JE, Pickman C, Rice A, Liebeskind JC, Holman EW (1980) Rewarding and aversive effects of morphine: temporal and pharmacological properties. Pharmacol Biochem Behav 13:501–505

Spyraki C, Fibiger HC, Phillips AG (1982a) Dopaminergic substrates of amphetamine-induced place preference conditioning. Brain Res 253:185–193

Spyraki C, Fibiger HC, Phillips AG (1982b) Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res 253:195–203

Spyraki C, Fibiger HC, Phillips AG (1983) Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology 79:278–283

Spyraki C, Kazandjian A, Varonos D (1985) Diazepam-induced place preference conditioning: appetitive and antiaversive properties. Psychopharmacology 87:225–232

Wise RA (1983) Neuroleptics and operant behavior: the anhedonia hypothesis. Behav Brain Sci 5:39–53

Received August 26, 1987 / Final version April 14, 1989